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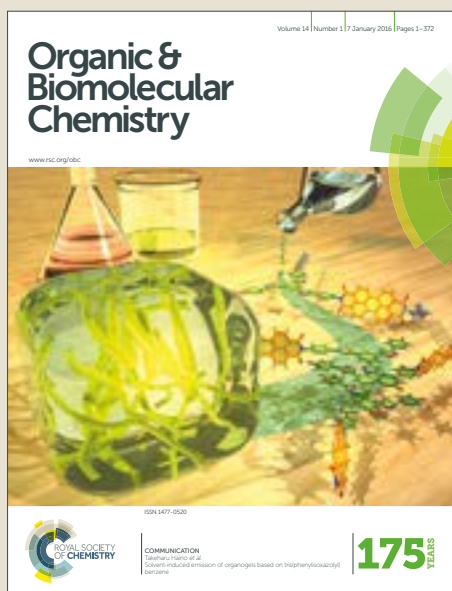
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Synthesis of highly substituted 2-spiropiperidines

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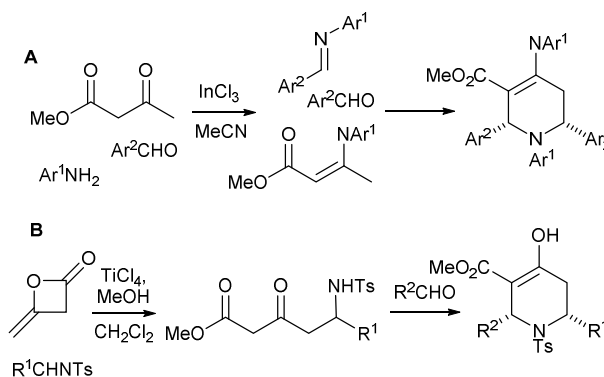
2-Spiropiperidines are a highly desirable, yet under represented structure in drug discovery. 2-Spiropiperidines were synthesised in either a two-pot or one-pot reaction. In the two-pot reaction, the addition of a Weiler dianion to *N*-Boc imines, followed by deprotection and *in situ* condensation with a cyclic ketone generated functionalised 2-spiropiperidines in good to excellent yields. In the one-pot reaction, the addition of Chan's diene to *N*-Boc imines under Maitland-Japp conditions, followed by the addition of sodium bicarbonate and a cyclic ketone formed functionalised 2-spiropiperidines in moderate to good yields.

Introduction

Spiropiperidines are an increasingly important structural unit, appearing in both natural products and drug discovery programs.¹ In the natural product arena they are present in several alkaloid classes, including histrionicotoxin,² nankakurine,³ pinnaic acid,⁴ etc. Within the context of drug discovery they are desired due to their well-defined conformations, and novel intellectual property value.⁵ For these reasons over the last few years an increasing number of routes for their synthesis have been described.^{1, 6} However, the majority of these routes are directed at providing access to 3- or 4-spiropiperidines, with limited methods available for the synthesis of 2-spiropiperidines.⁶ Those methods available for the formation of 2-spiropiperidines rely either on the use of toxic organotin-reagents,⁷ alkylation and reductive cyclisation of aminonitriles,⁸ or ring-closing metathesis,⁹ and often require the prior synthesis of advanced precursors.

We previously reported the synthesis of highly substituted piperidines *via* a modification of the Maitland-Japp tetrahydropyran synthesis; the replacement of an aldehyde with either an *N*-aryl^{10, 11} or *N*-tosyl imine.¹² *N*-Aryl imines were formed *in situ* from anilines and aryl ketones in the same pot as *N*-aryl enamines, formed by the condensation of anilines with β -ketoesters. The *N*-aryl- β -enaminoester underwent Stork enamine-like condensation¹³ with the *N*-aryl imines and cyclisation to form highly substituted piperidines (Scheme 1A).^{10, 11} *N*-Tosyl imines were reacted with diketene to form δ -amino- β -ketoesters which were treated *in situ* with an aldehyde to generate highly substituted non-symmetrical piperidines (Scheme 1B).¹² Given our previous contributions to the synthesis of piperidines and the increasing interest in the

synthesis of spiropiperidines, we decided to investigate the modification of these processes to enable the synthesis of 2-spiropiperidines.¹⁴



Scheme 1 Maitland-Japp syntheses of highly functionalised piperidines

Results and discussion

Initial investigations with *N*-tosyl imines

Due to the lack of availability of diketene, our initial study forced us to use the dianion of methyl acetoacetate,¹⁵ which was added to the *N*-tosyl imine of benzaldehyde **1**. It was hoped that the resultant δ -amino- β -ketoester **2**, which was formed in 44% yield could be cyclised onto a ketone (acetone) under Maitland-Japp conditions.^{12, 16} Treatment of δ -amino- β -ketoester **2** with acetone, TiCl_4 and pyridine in THF led only to the isolation of the Knoevenagel product **3** in 26% yield and re-isolated **2**. Submission of δ -amino- β -ketoester **3** to TiCl_4 in CH_2Cl_2 and stirring for an extended period of time led to elimination of tosyl amide, and the formation of **4**; no cyclisation to the piperidine was observed (Scheme 2). The identity of **4** was confirmed *via* its synthesis from δ -hydroxy- β -ketoester **6**. δ -Hydroxy- β -ketoester **6**¹⁷ was treated with Ac_2O , Et_3N , DMAP in CH_2Cl_2 at room temperature, which resulted in acylation of the hydroxyl and concomitant

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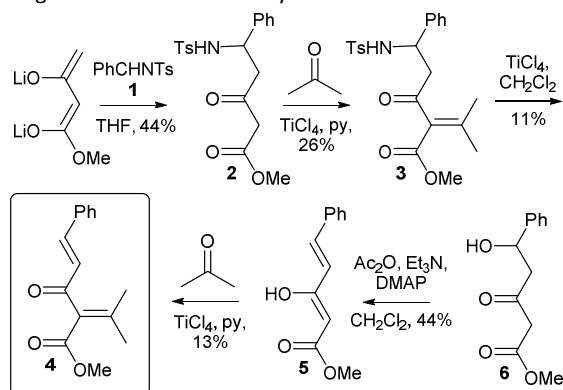
Electronic Supplementary Information (ESI) available: experimental procedures, copies of spectroscopic data. See DOI: 10.1039/x0xx00000x

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Journal Name

elimination of acetic acid. Enone **5** was then subjected to Maitland-Japp conditions (TiCl_4 , acetone, pyridine in THF) which led to the formation of **4** in 13% yield (Scheme 2), the spectroscopic data of which was identical to that formed through the elimination of tosyl amide from **3**.



Scheme 2 Attempted cyclisation with *N*-tosyl amine **2** and acetone

It was disheartening that cyclisation conditions which yielded piperidines with *N*-tosyl amines and aldehydes did not generate piperidines when ketones were used. We believe that this is due to a destabilising interaction in the transition state, not present in the cyclisation with aldehydes (Fig. 1). If cyclisation were to occur *via* **TS1** then there is a 1,3-diaxial interaction between the Ph-group and the axial Me-group. The alternative chair conformation **TS2** suffers from an $A_{1,2}$ -like destabilising interaction between the *N*-tosyl group and the equatorial Me-group.

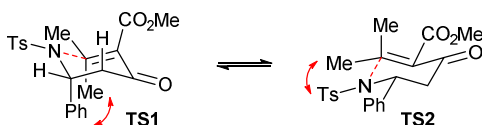


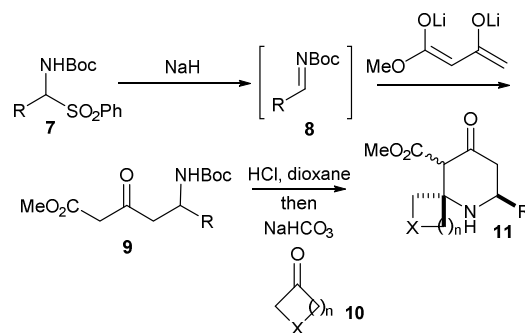
Fig 1 Destabilising interactions which disfavour cyclisation of **3**. Proton on *N* omitted for clarity

Attempts to deprotect **3** with Mg/MeOH ,¹⁸ and hence form the free amine for cyclisation, resulted in decomposition of the substrate and so the further use of *N*-tosyl imines was abandoned. Our attention turned to the use of *N*-Boc imines, which we reasoned could be synthesised efficiently and easily deprotected.

Two-pot synthesis of 2-spiropiperidines

Known aryl *N*-Boc imines were prepared from the appropriate aryl aldehyde according to literature procedures,¹⁹⁻²¹ and were isolated. These aryl *N*-Boc imines were treated with the Weiler dianion of methyl acetoacetate¹⁵ to generate δ -*N*-Boc-amino- β -ketoesters. Other *N*-Boc imines proved to be too unstable to be isolated and were generated *in situ* from their *N*-Boc sulfone precursor **7**. In these cases 3 eq. of NaH was used to form the *N*-Boc imine *in situ* before the addition of the Weiler dianion, which led to the formation of the δ -*N*-Boc-amino- β -ketoesters **9**. This procedure was so facile that it became our standard protocol for all *N*-Boc imines used, including those

which were stable enough to be isolated. It was found that these δ -*N*-Boc-amino- β -ketoesters **8** could be isolated and stored for several weeks without detriment. Cyclisation of δ -*N*-Boc-amino- β -ketoesters **8** was achieved by removal of the *N*-Boc group with HCl in dioxane to form the HCl salt. The HCl salt was "cracked" with NaHCO_3 in the presence of a ketone **9**, which promoted cyclisation and yielded the desired 2-spiropiperidine **10** (Scheme 3, Table 1 and Table 2).



Scheme 3 Two-step synthesis of 2-spiropiperidines **10**

Table 1 Synthesis of δ -*N*-Boc-amino- β -ketoesters **9**

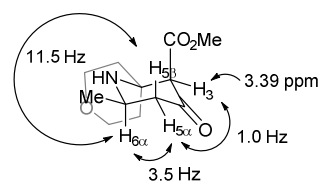
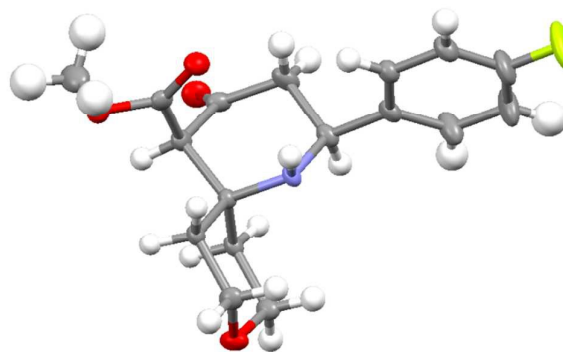
<i>N</i> -Boc sulfone 7	R	Yield 9 (%)
a	Me	76
b	Pr	65
c	iPr	50
d	Ph	73
e	4-FC ₆ H ₄	77
f	4-MeOC ₆ H ₄	53
g	3-pyridyl	56
h	methyl thiazole	58
i	<i>N</i> -methyl pyrazole	57
j	4-CNC ₆ H ₄	68

Table 2 Synthesis of 2-spiropiperidines 10

Entry	9 R	Ketone 10	Yield 11 (%)	dr ^a 11
a	a Me	acetone	85	2.5:1
b	a Me	cyclohexanone	85	7:1
c	a Me	cyclopentanone	43	5:1
d	a Me	cyclobutanone	57	2.5:1
e	a Me	4-pyranone	59	4.5:1
f	d Ph	cyclohexanone	78	7:1
g	e 4-FC ₆ H ₄	acetone	97	1.8:1
h	e 4-FC ₆ H ₄	cyclohexanone	75	5:1
i	e 4-FC ₆ H ₄	4-pyranone	56	2:1
j	e 4-FC ₆ H ₄	4-thiopyranone	63	1:1
k	f 4-MeOC ₆ H ₄	4-pyranone	33	2:1
l	g 3-pyridyl	acetone	86	1.5:1
m	g 3-pyridyl	4-pyranone	76	1.5:1
n	g 3-pyridyl	<i>N</i> -Cbz-4-piperidone	67	2:1
o	g 3-pyridyl	4-thiopyranone	75	0.95:1
p	h methyl thiazole	4-pyranone	75	1:1
q	i <i>N</i> -methyl pyrazole	4-pyranone	50	2.5:1
r	j 4-CNC ₆ H ₄	cyclobutanone	63	1:1
s	j 4-CNC ₆ H ₄	2-oxetanone	43	1.6:1

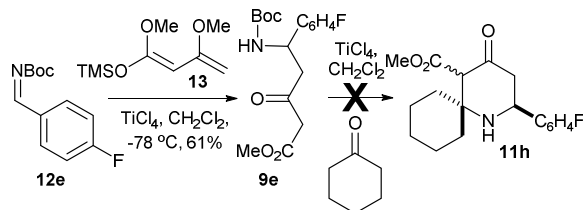
a) The ratio of diastereomers was determined by ¹H NMR analysis of the crude reaction mixture. In most cases the β-CO₂Me diastereomer dominated and is report first in the dr ratio.

A range of δ-*N*-Boc-amino-β-ketoesters **9** were prepared (Table 1) from *N*-Boc sulfone precursors **7** derived from aliphatic (**7a-c**) and aromatic aldehydes (**7d-j**), including several from the GSK aldehyde library.²² Aldehydes were selected after discussions with GSK, which highlighted compounds that would be of interest to medicinal chemists. Selected aldehyde derivatives included thiazole, pyrazole, pyridyl functionality and substituted aromatics (**7e-j**). All were isolated in good yields. Acetone and a selection of cyclic ketones (four to six membered rings), including *N*-, *O*- and *S*-heteroatom-containing cyclic ketones, all underwent smooth cyclisation with δ-*N*-Boc-amino-β-ketoesters **9** to form 2-spiropiperidines **11a-s** in good to excellent yields. The piperidines were formed as a mixture of diastereomeric methyl esters, and there was no evidence that the diastereomeric esters interconverted during isolation and purification. In most examples the major diastereomer was determined to have the axial β-ester group. In the representative case of **11e** H-3 (δ 3.39 ppm) displayed a 'W-coupling' of 1.0 Hz to H-5α (δ 2.64 ppm) indicating both their equatorial positions. A coupling constant of 3.5 Hz was seen between H-5α and H-6α indicating a *syn*-relationship, while there was an 11.5 Hz coupling between H-6α and H-5β (δ 3.06 ppm) indicating an *anti*-relationship (Fig 2). This stereochemical arrangement was confirmed by an X-ray crystal structure of **11i**[†] (Fig. 3). Presumably the ester group is axial to avoid a destabilising steric interaction with the protons on the adjacent spiro-ring.

Fig 2 ¹H NMR data supporting the formation of **11e** β-CO₂Me diastereomerFig 3 X-ray crystal structure of **11i** showing the axial methyl ester[†]

One-pot synthesis of 2-spiropiperidines

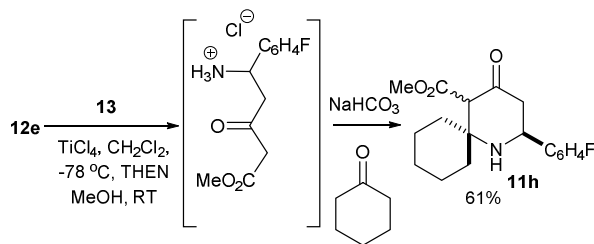
With a two-pot procedure for the synthesis of 2-spiropiperidines realised, attention turned to the re-development of a one-pot procedure. Previous studies had led to the development of a one-pot Maitland-Japp synthesis of piperidines¹² (Scheme 1B), however; the lack of availability of diketene necessitated the use of an alternative nucleophile. As one variant of the one-pot Maitland-Japp synthesis of tetrahydropyrans (THPs) had utilised the *bis*-silyl enoether of methyl acetoacetate¹⁷ (Chan's diene **13**) it was decided to investigate this as the nucleophile. It was also decided to investigate the addition and cyclisation steps independently at first in order to ensure both reactions were viable. As TiCl₄ had promoted the addition of Chan's diene to aldehydes, that was examined first. It was found that TiCl₄ promoted the addition of Chan's diene to *N*-Boc imine **11e** to form δ-*N*-Boc-amino-β-ketoester **9e** in 61% yield. However, submission of **9e** to TiCl₄ in the presence of cyclohexanone did not result in cyclisation at either -78 °C or RT, and only the re-isolation of **9e** (Scheme 4).

Scheme 4: Attempted one-pot synthesis of 2-spiropiperidine **10h**

ARTICLE

Journal Name

It was rationalised that the *N*-Boc group was inhibiting the cyclisation both electronically and sterically, and we were somewhat surprised that it remained intact in the presence of TiCl_4 at RT. To solve this problem and develop a one-pot method, conditions had to be devised to affect removal of the *N*-Boc group under conditions compatible with both the Mannich-like addition and cyclisation reactions. It was rationalised that the addition of MeOH to the reaction after the formation of **9e** would generate HCl by methanolysis of the TiCl_4 . The HCl generated *in situ* would remove the *N*-Boc group, revealing the amine as the HCl salt. At this stage, addition of a base and a ketone should free the amine and initiate cyclisation to **11h**.¹⁴ Indeed, when **12e** was treated with Chan's diene and TiCl_4 at -78°C , Mannich-like addition occurred to generate **9e** (by TLC). At this point MeOH was introduced to the reaction and the temperature was raised to RT. After a short while both cyclohexanone and NaHCO_3 were added to the reaction and stirred at RT. This procedure yielded **11h** after work up and purification in 61% yield (Scheme 5). It is worth noting that the two-step procedure yielded **11h** in 57% yield over the two steps.

Scheme 5 Successful one-pot synthesis of 2-spiropiperidine **10h**

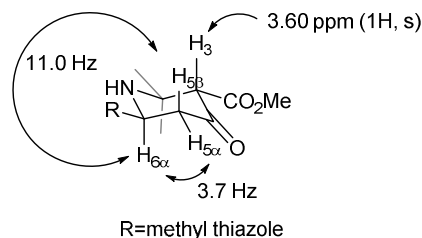
With a one-pot procedure developed its scope was explored using several different δ -*N*-Boc-imines **12** and ketones **10** (Table 3). For the majority of cases (entry 1-4, 6 and 7) the one-pot reaction generated 2-spiropiperidines in moderate to good yields, and in examples **11h**, **11i**, **11k** and **11p** these were higher yields than for the two-pot procedure. 2-Spiropiperidines **11t**, **11u**, **11v**, **11w** and **11x** (entries 6-10) had not been synthesised previously by the two-pot method. In the cases of entries 7 and 8, the diastereomeric ratio of **11u** and **11v** had to be determined after silica plug filtration due to the overlapping peaks of some impurities.

Table 3 One-pot synthesis of 2-spiropiperidines **10**

Entry	Ar 12	Ketone 10	Yield 11 (%)	dr ^a 11
1	e p-FC ₆ H ₄	cyclohexanone	h 61	5:1
2	e p-FC ₆ H ₄	4-pyranone	i 69	2:1
3	f p-MeOC ₆ H ₄	4-pyranone	k 62	1.5:1
4	h methyl thiazole	4-pyranone	p 49	2.5:1
5	j 4-CNC ₆ H ₄	cyclobutanone	r 37	3.5:1
6	h methyl thiazole	4-thiopyranone	t 55	3:1
7	h methyl thiazole	<i>N</i> -Cbz-4-piperidone	u 45	2.5:1 ^b
8	j 4-CNC ₆ H ₄	<i>N</i> -Cbz-4-piperidone	v 24	4:1 ^b
9	k 4-CF ₃ C ₆ H ₄	cyclohexanone	w 28	1.5:1
10	h methyl thiazole	acetone	x 24	1:1.5 ^c

a) The ratio of diastereomers was determined by ¹H NMR analysis of the crude reaction mixture. In most cases the β -CO₂Me diastereomer dominated and is report first in the dr ratio. b) The ratio of diastereomers was determined by ¹H NMR analysis after silica plug chromatography. c) α -CO₂Me was the major diastereomer.

Interestingly the major product in the formation of **11x** (entry 10) was the α -CO₂Me diastereomer. The diastereomeric ratio did not change upon resubmission to the reaction conditions. The configuration of this diastereomer was determined by comparison of the chemical shifts of H3 and H5 β , along with their coupling constants. The proton H3 (δ 3.60 ppm) appeared as a singlet and at a chemical shift reminiscent of the minor diastereomers formed in other examples. The proton assigned as H5 β had a chemical shift of δ 2.40 ppm and a coupling constant of 11.0 Hz to H6 α , indicating their *trans*-diaxial relationship (Fig 4).

Fig 4 ¹H NMR data supporting the formation of **11x** α -CO₂Me diastereomer

Conclusions

Simple and robust two-pot and one-pot procedures for the synthesis of 2-spiropiperidines have been developed. These methods are applicable to a large range of differently functionalised 2-spiropiperidines, and allow for the synthesis

of piperidines spirofused to 4-, 5-, and 6-membered carbo- and heterocyclic rings and substituted at the C3 and C6 positions of the piperidine ring. The ease of these procedures will allow the evaluation of 2-spiropiperidines in drug discovery programs and they will be of use in the synthesis of spirocyclic alkaloid natural products.

Experimental

General

Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Where a solvent is described as "dry" it was purified by PureSolv alumina columns from Innovative Technologies. Melting points were determined using a Stuart SMP3 apparatus. Infra-red spectra were acquired on a Thermo Nicolet Avatar 370 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400, a Jeol 500 Avance III HD 500 or a Jeol AV500 at ambient temperature. Coupling constants (J) are quoted in Hertz. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F₂₅₄. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate or basic aqueous potassium permanganate. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich.

General procedure for the synthesis of benzenesulfonyl carbamic esters 7²¹

To a solution of aldehyde (53.6 mmol) in water, methanol and formic acid (2:1:0.7, 142 mL) was added *tert*-butyl carbamate (35.7 mmol) and benzenesulfinic acid sodium salt (71.4 mmol). The mixture was stirred at room temperature for 3 days. The precipitate was filtered and washed with water (150 mL) and hexane (300 mL).

(1-Benzenesulfonyl-ethyl)-carbamic acid *tert*-butyl ester (7a)

Acetaldehyde (3 mL, 53.6 mmol) yielded 8.27 g (81%) as a white solid. Spectroscopic data was identical to that previously reported.²³ mp 129–131 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.94–7.85 (m, 2H), 7.66–7.58 (m, 1H), 7.57–7.48 (m, 2H), 5.08 (d, J = 10.5 Hz, 1H), 4.99 (dq, J = 10.5, 7.0 Hz, 1H), 1.62 (d, J = 7.0 Hz, 3H), 1.20 (s, 9H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 153.5, 136.7, 134.0, 129.5, 129.2, 80.9, 66.9, 28.1, 13.0 ppm; IR (ATR): ν_{\max} 3337, 2973, 1691, 1518, 1313, 1145 cm⁻¹; HRMS (ESI) 308.0918 (M + Na⁺. C₁₃H₁₉NNaO₄S requires 308.0927).

(1-Benzenesulfonyl-butyl)-carbamic acid *tert*-butyl ester (7b)

Butyraldehyde (1.15 mL, 12.8 mmol) yielded 1.33 g (50%) as a white solid; mp 117–118 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.91–

7.86 (m, 2H), 7.62–7.56 (m, 1H), 7.54–7.47 (m, 2H), 5.07 (d, J = 11.0 Hz, 1H), 4.84 (td, J = 11.0, 3.5 Hz, 1H), 2.24–2.13 (m, 1H), 1.79–1.65 (m, 1H), 1.62–1.48 (m, 1H), 1.46–1.35 (m, 1H), 1.24 (s, 9H), 0.95 (t, J = 7.5 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 153.9, 137.1, 133.9, 129.4, 129.1, 80.8, 70.7, 28.3, 28.1, 18.8, 13.6 ppm; IR (ATR): ν_{\max} 3286, 2960, 2874, 1690, 1526, 1310, 1246, 1144, 1083 cm⁻¹; HRMS (ESI) 336.1243 (M + Na⁺. C₁₅H₂₃NNaO₄S requires 336.1240).

(1-Benzenesulfonyl-2-methyl-propyl)-carbamic acid *tert*-butyl ester (7c)

Isobutyraldehyde (4.67 mL, 51.3 mmol) yielded 4.93 g (47%) as a white solid. Spectroscopic data was identical to that previously reported.²⁴ mp 116–117.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.91–7.86 (m, 2H), 7.64–7.58 (m, 1H), 7.55–7.49 (m, 2H), 5.14 (d, J = 11.0 Hz, 1H), 4.84 (dd, J = 11.0, 3.5 Hz, 1H), 2.82–2.73 (m, 1H), 1.22 (s, 9H), 1.14 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 154.2, 138.2, 133.8, 129.2, 129.1, 80.9, 74.4, 28.1, 26.8, 20.8, 17.0 ppm; IR (ATR): ν_{\max} 3356, 3232, 3142, 2965, 1704, 1364, 1307, 1141, 1082 cm⁻¹; HRMS (ESI) 226.1404 (M + Na⁺. C₁₀H₂₁NNaO₃ requires 226.1414 for the methanol adduct (-SO₂Ph, +OMe)).

(Benzenesulfonyl-phenyl-methyl)-carbamic acid *tert*-butyl ester (7d)

Benzaldehyde (1.52 mL, 15 mmol) yielded 3.26 g (94%) as a white solid. Spectroscopic data was identical to that previously reported.¹⁹ mp 158–161 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.92 (d, J = 7.5 Hz, 2H), 7.64 (dd, J = 7.5, 7.5 Hz, 1H), 7.53 (dd, J = 7.5, 7.5 Hz, 2H), 7.48–7.39 (m, 5H), 5.94 (d, J = 10.5 Hz, 1H), 5.87 (d, J = 10.5 Hz, 1H), 1.25 (s, 9H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 153.6, 137.0, 134.1, 130.0, 129.6, 129.2, 129.1, 128.9, 125.1, 81.4, 74.0, 28.1 ppm; IR (ATR): ν_{\max} 3355, 3274, 2978, 1693, 1508, 1306, 1141 cm⁻¹; HRMS (ESI) 260.1257 (M + Na⁺. C₁₃H₁₉NNaO₃ requires 260.1257 for the methanol adduct (-SO₂Ph, +OMe)).

[Benzenesulfonyl-(4-fluoro-phenyl)-methyl]-carbamic acid *tert*-butyl ester (7e)

4-Fluorobenzaldehyde (9.61 mL, 90.0 mmol) yielded 19.9 g (91%) as a white solid. Spectroscopic data was identical to that previously reported.¹⁹ mp 167–170 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.95–7.86 (m, 2H), 7.69–7.61 (m, 1H), 7.58–7.51 (m, 2H), 7.48–7.39 (m, 2H), 7.13–7.05 (m, 2H), 5.94 (d, J = 10.5 Hz, 1H), 5.85 (d, J = 10.5 Hz, 1H), 1.24 (s, 9H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 163.7 (d, J = 251 Hz), 153.6, 136.8, 134.2, 131.0 (d, J = 8.5 Hz), 129.6, 129.2, 125.9 (d, J = 3.5 Hz), 116.0 (d, J = 21.5 Hz), 81.5, 73.3, 28.1 ppm; ¹⁹F NMR (376 MHz, CDCl₃): δ -110.7 ppm; IR (ATR): ν_{\max} 3367, 2972, 1703, 1506, 1309, 1140 cm⁻¹; HRMS (ESI) 278.1150 (M + Na⁺. C₁₃H₁₈FNNaO₃ requires 278.1163 for the methanol adduct (-SO₂Ph, +OMe)).

[Benzenesulfonyl-(4-methoxy-phenyl)-methyl]-carbamic acid *tert*-butyl ester (7f)

4-Anisaldehyde (3.85 mL, 31.7 mmol) yielded 5.63 g (71%) as a white solid. Spectroscopic data was identical to that previously

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reported.¹⁹ mp 156–158 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.05–7.97 (m, 2H), 7.67–7.59 (m, 1H), 7.57–7.49 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.88 (d, *J* = 10.5 Hz, 1H), 5.76 (d, *J* = 10.5 Hz, 1H), 3.82 (s, 3H), 1.24 (s, 9H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 160.4, 153.2, 137.1, 134.0, 130.3, 129.6, 129.2, 121.8, 114.4, 81.3, 73.6, 55.5, 28.1 ppm; IR (ATR): ν_{\max} 3361, 2967, 1695, 1503, 1310, 1162, 1149 cm⁻¹; HRMS (ESI) 290.1350 (*M* + Na⁺. C₁₄H₂₁NNaO₄ requires 290.1363 for the methanol adduct (-SO₂Ph, +OMe)).

(Benzenesulfonyl-pyridin-3-yl-methyl)-carbamic acid tert-butyl ester (7g)

Nicotinaldehyde (7.8 mL, 83.0 mmol) yielded 9.09 g (47%) as a white solid. Spectroscopic data was identical to that previously reported.²⁵ mp 168.5–171 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.68 (dd, *J* = 5.0, 1.5 Hz, 1H), 8.66 (br d, *J* = 1.5 Hz, 1H) 7.96–7.90 (m, 2H), 7.85 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 1H), 7.68 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.57 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.38 (dd, *J* = 8.0, 5.0 Hz, 1H), 6.03 (d, *J* = 10.5 Hz, 1H), 5.98 (d, *J* = 10.5 Hz, 1H), 1.25 (s, 9H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 153.6, 151.0, 150.1, 136.5, 136.4, 134.5, 129.6, 129.4, 126.4, 123.7, 81.8, 72.0, 28.1 ppm; IR (ATR): ν_{\max} 3200, 3064, 2979, 1716, 1531, 1303, 1140 cm⁻¹; HRMS (ESI) 239.1392 (*M* + H⁺. C₁₂H₁₉N₂O₃ requires 239.1390 for the methanol adduct (-SO₂Ph, +OMe)).

[Benzenesulfonyl-(4-methyl-thiazol-5-yl)-methyl]-carbamic acid tert-butyl ester (7h)

4-Methylthiazole-5-carbaldehyde (6.68 g, 52.5 mmol) yielded 6.70 g (52%) as an off-white solid; mp 167–169 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.80 (s, 1H), 7.93–7.87 (m, 2H), 7.67 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.57 (dd, *J* = 7.5, 7.5 Hz, 2H), 6.26 (d, *J* = 10.5 Hz, 1H), 5.59 (d, *J* = 10.5 Hz, 1H), 3.42 (s, 3H), 1.27 (s, 9H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 154.5, 153.5, 153.3, 136.2, 134.5, 129.6, 129.4, 121.1, 81.9, 68.4, 28.1, 15.7 ppm; IR (ATR): ν_{\max} 3153, 3071, 2976, 1707, 1535, 1302, 1140 cm⁻¹; HRMS (ESI) 259.1114 (*M* + H⁺. C₁₁H₁₉N₂O₃ requires 259.1111 for the methanol adduct (-SO₂Ph, +OMe)).

[Benzenesulfonyl-(1-methyl-1H-pyrazol-4-yl)-methyl]-carbamic acid tert-butyl ester (7i)

1-Methyl-1H-pyrazole-4-carbaldehyde (1.5 g, 13.6 mmol) yielded 1.42 g (71%) as a white solid; mp 153.7–156.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.95–7.89 (m, 2H), 7.66 (s, 1H), 7.66–7.59 (m, 2H), 7.54 (dd, *J* = 7.5, 7.5 Hz, 2H), 5.95 (d, *J* = 10.5 Hz, 1H), 5.73 (d, *J* = 10.5 Hz, 1H), 3.92 (s, 3H), 1.21 (s, 9H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 153.5, 138.9, 136.6, 134.2, 130.7, 129.7, 129.2, 125.0, 81.3, 67.4, 39.4, 28.1 ppm; IR (ATR): ν_{\max} 3359, 2971, 1709, 1521, 1303, 1148, 1136 cm⁻¹; HRMS (ESI) 264.1305 (*M* + Na⁺. C₁₁H₁₉N₃NaO₃ requires 264.1319 for the methanol adduct (-SO₂Ph, +OMe)).

[Benzenesulfonyl-(4-cyano-phenyl)-methyl]-carbamic acid tert-butyl ester (7j)

4-Cyanobenzaldehyde (8.40 g, 64.1 mmol) yielded 14.9 g (94%) as a white solid. Spectroscopic data was identical to that previously reported.²⁰ mp 151–154 °C; ¹H NMR (400 MHz,

CDCl₃): δ 7.92 (d, *J* = 7.5 Hz, 2H), 7.73–7.64 (m, 3H), 7.62–7.53 (m, 4H), 6.00 (d, *J* = 10.5 Hz, 1H), 5.93 (d, *J* = 10.5 Hz, 1H), 1.24 (s, 9H) ppm; ¹³C NMR (101 MHz, CDCl₃): δ 153.5, 136.4, 135.1, 134.6, 132.5, 129.8, 129.6, 129.4, 118.2, 113.8, 81.9, 77.4, 28.1 ppm; IR (ATR): ν_{\max} 3369, 2962, 2235, 1701, 1506, 1308, 1143 cm⁻¹; HRMS (ESI) 285.1213 (*M* + Na⁺. C₁₄H₁₈N₂NaO₃ requires 285.1210 for the methanol adduct (-SO₂Ph, +OMe)).

General procedure for the synthesis of *N*-Boc-δ-amino-β-ketoesters 9

To a solution of diisopropylamine (21.0 mmol) in THF (30 mL) at -78 °C was added *n*-BuLi (2.5M in hexanes, 21.0 mmol). The solution was stirred for 10 mins at -78 °C then a further 5 mins at room temperature. A solution of methyl acetoacetate (10.5 mmol) in THF (6 mL) was added over 10 mins at -78 °C, then stirred for a further 40 mins. The imine was prepared by the portionwise addition of sulfone (3.50 mmol) to a suspension of NaH (7.00 mmol) in THF (12 mL) at room temperature. The subsequent mixture was stirred for 20 mins, then immediately transferred to the dianion mixture at -50 °C. The reaction was stirred for 30 mins, then quenched with 10 M acetic acid in THF (2.5 mL). The mixture was warmed to room temperature and concentrated *in vacuo*. The residue was partitioned between EtOAc (30 mL) and water (25 mL). The aqueous layer was extracted with EtOAc (2 x 25 mL). Organics were combined, washed with water (50 mL) and brine (50 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate/hexane) to afford the protected δ-amino-β-ketoester.

5-tert-Butoxycarbonylamino-3-oxo-hexanoic acid methyl ester (9a)

Sulfone **7a** (1.00 g, 3.50 mmol) yielded 681 mg (76%) as a white solid after column chromatography (20% EtOAc/hexane); mp 55–56 °C; ¹H NMR (400 MHz, CDCl₃): δ 4.80 (br s, 1H), 4.08–3.94 (m, 1H), 3.72 (s, 3H), 3.49 (d, *J* = 15.5 Hz, 1H), 3.43 (d, *J* = 15.5 Hz, 1H), 2.79 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.69 (dd, *J* = 17.0, 5.5 Hz, 1H), 1.41 (s, 9H), 1.20 (d, *J* = 7.0 Hz, 3H) ppm; ¹³C-NMR (101 MHz, CDCl₃): δ 201.6, 167.6, 155.2, 79.5, 52.5, 49.4, 49.1, 43.3, 28.5, 20.6 ppm; IR (ATR): ν_{\max} 3366, 3312, 3000, 2976, 1737, 1702, 1679, 1535 cm⁻¹; HRMS (ESI) 282.1321 (*M* + Na⁺. C₁₂H₂₁NNaO₅ requires 282.1312).

5-tert-Butoxycarbonylamino-3-oxo-octanoic acid methyl ester (9b)

Sulfone **7b** (400 mg, 1.28 mmol) yielded 238 mg (65%) as a white solid after column chromatography (20% EtOAc/hexane); mp 53–55 °C; ¹H NMR (400 MHz, CDCl₃): δ 4.78 (d, *J* = 7.5 Hz, 1H), 3.95–3.79 (m, 1H), 3.72 (s, 3H), 3.50 (d, *J* = 15.5 Hz, 1H), 3.43 (d, *J* = 15.5 Hz, 1H), 2.73 (d, *J* = 5.5 Hz, 2H), 1.52–1.22 (m, 4H), 1.40 (s, 9H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm; ¹³C-NMR (101 MHz, CDCl₃): δ 201.9, 167.6, 155.6, 79.4, 52.5, 49.4, 47.7, 47.3, 36.8, 28.5, 19.5, 13.9 ppm; IR (ATR): ν_{\max} 3288, 2964, 2933, 1742, 1704, 1679, 1539, 1262, 1173 cm⁻¹; HRMS (ESI) 310.1636 (*M* + Na⁺. C₁₄H₂₅NNaO₅ requires 310.1625).

5-tert-Butoxycarbonylamino-6-methyl-3-oxo-heptanoic acid methyl ester (9c)

Sulfone **7c** (2.00 g, 6.39 mmol) yielded 917 mg (50%) as a white solid after column chromatography (20% EtOAc/hexane); mp 60–62 °C; ^1H NMR (400 MHz, CDCl_3): δ 4.75 (br d, J = 9.0 Hz, 1H), 3.81–3.71 (m, 1H), 3.73 (s, 3H), 3.56 (d, J = 16.0 Hz, 1H), 3.47 (d, J = 16.0 Hz, 1H), 2.77 (dd, J = 16.0, 4.5 Hz, 1H), 2.69 (dd, J = 16.0, 7.0 Hz, 1H), 1.91–1.79 (m, 1H), 1.42 (s, 9H), 0.90 (d, J = 7.0 Hz, 6H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 202.0, 167.7, 155.7, 79.4, 52.7, 52.4, 49.0, 45.6, 31.8, 28.4, 19.5, 18.6 ppm; IR (ATR): ν_{max} 3356, 2974, 2958, 1748, 1713, 1686, 1525, 1307, 1128 cm^{-1} ; HRMS (ESI) 310.1618 ($\text{M} + \text{Na}^+$, $\text{C}_{14}\text{H}_{25}\text{NNaO}_5$ requires 320.1625).

5-tert-Butoxycarbonylamino-3-oxo-5-phenyl-pentanoic acid methyl ester (9d)

Sulfone **7d** (1.00 g, 2.89 mmol) yielded 672 mg (73%) as a white solid after column chromatography (20% EtOAc/hexane); mp 83.7–85.5 °C; ^1H NMR (500 MHz, CDCl_3): δ 7.34–7.22 (m, 5H), 5.34 (br s, 1H), 5.10 (br s, 1H), 3.68 (s, 3H), 3.42 (d, J = 15.5 Hz, 1H), 3.38 (d, J = 15.5 Hz, 1H), 3.17 (dd, J = 16.5, 6.0 Hz, 1H), 3.04 (dd, J = 16.5, 6.0 Hz, 1H), 1.41 (s, 9H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 200.9, 167.4, 155.2, 141.2, 128.8, 127.7, 126.3, 79.9, 52.5, 51.0, 49.5, 48.8, 28.4 ppm; IR (ATR): ν_{max} 3393, 2978, 1752, 1718, 1681, 1170, 1152 cm^{-1} ; HRMS (ESI) 344.1463 ($\text{M} + \text{Na}^+$, $\text{C}_{17}\text{H}_{23}\text{NNaO}_5$ requires 344.1468).

5-tert-Butoxycarbonylamino-5-(4-fluoro-phenyl)-3-oxo-pentanoic acid methyl ester (9e)

Sulfone **7e** (5.00 g, 13.7 mmol) yielded 3.59 g (77%) as a white solid after column chromatography (15–20% EtOAc/hexane); mp 87–88.5 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.30–7.23 (m, 2H), 7.05–6.97 (m, 2H), 5.33 (br s, 1H), 5.13–5.01 (m, 1H), 3.69 (s, 3H), 3.42 (d, J = 15.5 Hz, 1H), 3.38 (d, J = 15.5 Hz, 1H), 3.16 (dd, J = 17.0, 6.0 Hz, 1H), 3.02 (dd, J = 17.0 Hz, 6.0 Hz, 1H), 1.41 (s, 9H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 200.7, 167.4, 162.1 (d, J = 247.0 Hz), 155.2, 137.2, 128.1 (d, J = 8.0 Hz), 115.6 (d, J = 21.5 Hz), 80.1, 52.6, 50.4, 49.5, 48.7, 28.4 ppm; ^{19}F NMR (376 MHz, CDCl_3): δ -116.7 ppm; IR (ATR): ν_{max} 3306, 2982, 1741, 1713, 1673, 1535, 1511, 1365, 1328, 1286, 1221, 1161, 999 cm^{-1} ; HRMS (ESI) 340.1556 ($\text{M} + \text{H}^+$, $\text{C}_{17}\text{H}_{23}\text{FNO}_5$ requires 340.1555).

5-tert-Butoxycarbonylamino-5-(4-methoxy-phenyl)-3-oxo-pentanoic acid methyl ester (9f)

Sulfone **7f** (3.00 g, 7.95 mmol) yielded 1.49 g (53%) as a yellow oil after column chromatography (15–20% EtOAc/hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.24–7.19 (m, 2H), 6.89–6.84 (m, 2H), 5.20 (br s, 1H), 5.11–5.01 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.43 (d, J = 16.0 Hz, 1H), 3.41 (d, J = 16.0 Hz, 1H), 3.15 (dd, J = 16.5, 6.5 Hz, 1H), 3.05 (dd, J = 16.5, 6.5 Hz, 1H), 1.42 (s, 9H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 200.7, 167.3, 159.0, 155.0, 133.3, 127.4, 114.1, 79.8, 55.3, 52.4, 50.5, 49.4, 48.8, 28.3 ppm; IR (ATR): ν_{max} 3356, 2974, 2839, 1748, 1708, 1679, 1512,

1243, 1163, 1037 cm^{-1} ; HRMS (ESI) 352.1743 ($\text{M} + \text{H}^+$, $\text{C}_{18}\text{H}_{26}\text{NO}_6$ requires 352.1755).

5-tert-Butoxycarbonylamino-3-oxo-5-pyridin-3-yl-pentanoic acid methyl ester (9g)

Sulfone **7g** (5.00 g, 14.4 mmol) yielded 2.58 g (56%) as an off-white solid after column chromatography (100% ethyl acetate); mp 96.5–99.5 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.58–8.54 (m, 1H), 8.50 (dd, J = 4.5, 1.5 Hz, 1H), 7.64 (ddd, J = 8.0, 1.5, 1.5 Hz, 1H), 7.26 (dd, J = 8.0, 4.5 Hz, 1H), 5.51 (br s, 1H), 5.13 (br s, 1H), 3.69 (s, 3H), 3.45 (d, J = 15.5 Hz, 1H), 3.40 (d, J = 15.5 Hz, 1H), 3.24 (dd, J = 17.0, 4.0 Hz, 1H), 3.08 (dd, J = 17.0, 4.0 Hz, 1H), 1.41 (s, 9H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 200.6, 167.3, 155.1, 148.9, 148.2, 136.9, 134.2, 123.5, 80.3, 52.6, 49.3, 48.8, 48.1, 28.4 ppm; IR (ATR): ν_{max} 3208, 2982, 1756, 1709, 1542, 1365, 1282, 1178, 1082, 1005 cm^{-1} ; HRMS (ESI) 323.1594 ($\text{M} + \text{H}^+$, $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_5$ requires 323.1601).

5-tert-Butoxycarbonylamino-5-(4-methyl-thiazol-5-yl)-3-oxo-pentanoic acid methyl ester (9h)

Sulfone **7h** (5.00 g, 13.6 mmol) yielded 2.69 g (58%) as a pale red solid after column chromatography (50–100% ethyl acetate/hexane); mp 91.5–94 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.60 (s, 1H), 5.41 (dd, J = 14.0, 6.0 Hz, 1H), 5.27 (br s, 1H), 3.71 (s, 3H), 3.46 (d, J = 15.5 Hz, 1H), 3.42 (d, J = 15.5 Hz, 1H), 3.21 (dd, J = 17.5, 6.0 Hz, 1H), 3.06 (dd, J = 17.5, 6.0 Hz, 1H), 2.49 (s, 3H), 1.41 (s, 9H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 200.2, 167.2, 154.8, 150.5, 149.9, 132.7, 80.4, 52.7, 51.5, 49.4, 44.5, 28.4, 15.5 ppm; IR (ATR): ν_{max} 3214, 2976, 1752, 1719, 1701, 1532, 1277, 1172, 1127, 1003 cm^{-1} ; HRMS (ESI) 343.1314 ($\text{M} + \text{Na}^+$, $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_5\text{S}$ requires 343.1322).

5-tert-Butoxycarbonylamino-5-(1-methyl-1H-pyrazol-4-yl)-3-oxo-pentanoic acid methyl ester (9i)

Sulfone **7i** (1.3 g, 3.51 mmol) yielded 652 mg (57%) as a colourless oil after column chromatography (50–100% ethyl acetate/hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.37 (s, 1H), 7.30 (s, 1H), 5.22 (br s, 1H), 5.12–5.03 (m, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.48 (d, J = 15.5 Hz, 1H), 3.44 (d, J = 15.5 Hz, 1H), 3.12 (dd, J = 17.0, 6.0 Hz, 1H), 3.05 (dd, J = 17.0, 6.0 Hz, 1H), 1.44 (s, 9H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 201.1, 167.4, 155.2, 137.2, 128.4, 122.5, 79.9, 52.5, 49.4, 48.4, 43.0, 39.1, 28.4 ppm; IR (ATR): ν_{max} 3355, 2976, 1744, 1705, 1512, 1365, 1245, 1162, 1015 cm^{-1} ; HRMS (ESI) 326.1697 ($\text{M} + \text{H}^+$, $\text{C}_{15}\text{H}_{24}\text{N}_3\text{O}_5$ requires 326.1711).

5-tert-Butoxycarbonylamino-5-(4-cyano-phenyl)-3-oxo-pentanoic acid methyl ester (9j)

Sulfone **7j** (2.00 g, 5.38 mmol) yielded 1.26 g (68%) as a white solid after column chromatography (15–25% EtOAc/hexane); mp 93–95.5 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.64–7.60 (m, 2H), 7.45–7.40 (m, 2H), 5.53 (br s, 1H), 5.13 (br s, 1H), 3.70 (s, 3H), 3.43 (d, J = 15.5 Hz, 1H), 3.38 (d, J = 15.5 Hz, 1H), 3.22 (dd, J = 17.5, 4.5 Hz, 1H), 3.05 (dd, J = 17.5, 4.5 Hz, 1H), 1.41 (s, 9H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 200.3, 167.3, 155.1, 147.0, 132.6, 127.2, 118.8, 111.4, 80.4, 52.7, 50.5, 49.3, 47.9, 28.4

ppm; IR (ATR): ν_{\max} 3343, 2995, 2955, 2228, 1751, 1707, 1676, 1525, 1271, 1249, 1166, 1152 cm^{-1} ; HRMS (ESI) 369.1421 ($M + \text{Na}^+$. $\text{C}_{18}\text{H}_{22}\text{N}_2\text{NaO}_5$ requires 369.1421).

General procedure for the synthesis of 2-spiropiperidines 11

Protected δ -amino- β -ketoester (3.00 mmol) was stirred in 4M HCl in dioxane (45.0 mmol) for 3h at room temperature. The mixture was concentrated *in vacuo* to afford the hydrochloride salt which was used without further purification.

To a suspension of hydrochloride salt (0.308 mmol) and ketone (1.54 mmol) in CH_2Cl_2 (1 mL), was added NaHCO_3 (129 mg, 1.54 mmol). The reaction was stirred for 16h at room temperature, then filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford 2-spiropiperidin-4-ones.

2,2,6-Trimethyl-4-oxo-piperidine-3-carboxylic acid methyl ester (11a)

Hydrochloride salt of **9a** (60 mg, 0.308 mmol) yielded 52 mg (85%, 2.5:1 dr) as a yellow oil without further purification; ^1H NMR (500 MHz, CDCl_3): δ 3.69 (s, 3H), 3.22 (d, $J = 1.0$ Hz, 1H), 3.18 (dq, $J = 10.5$, 6.5, 3.5 Hz, 1H), 2.47 (dd, $J = 13.5$, 10.5 Hz, 1H), 2.32 (ddd, $J = 13.5$, 3.5, 1.0 Hz, 1H), 1.26 (d, $J = 6.5$ Hz, 3H), 1.18 (s, 3H), 1.09 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 205.7, 169.7, 66.8, 57.9, 52.3, 48.4, 46.9, 28.2, 26.1, 22.8 ppm; IR (ATR): ν_{\max} 2967, 1705, 1610, 1534, 1434, 1136 cm^{-1} ; HRMS (ESI) 200.1289 ($M + \text{H}^+$. $\text{C}_{10}\text{H}_{18}\text{NO}_3$ requires 200.1281).

2-Methyl-4-oxo-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11b)

Hydrochloride salt of **9a** (60 mg, 0.308 mmol) yielded 63 mg (85%, 7:1 dr) as a yellow oil. Aqueous work-up was performed, partitioning between ethyl acetate and 2N aq. NaOH; ^1H NMR (500 MHz, CDCl_3): δ 3.67 (s, 3H), 3.34 (br s, 1H), 3.15 (dq, $J = 10.5$, 6.5, 3.5 Hz, 1H), 2.51 (dd, $J = 13.5$, 10.5 Hz, 1H), 2.30 (ddd, $J = 13.5$, 3.5, 1.0 Hz, 1H), 1.60-1.30 (m, 10H), 1.25 (d, $J = 6.5$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 206.1, 169.5, 65.8, 60.3, 52.1, 47.5, 47.2, 36.6, 33.7, 25.8, 22.9, 21.6, 21.1 ppm; IR (ATR): ν_{\max} 2930, 2856, 1703, 1434, 1327, 1161 cm^{-1} ; HRMS (ESI) 240.1592 ($M + \text{H}^+$. $\text{C}_{13}\text{H}_{22}\text{NO}_3$ requires 240.1594).

7-Methyl-9-oxo-6-aza-spiro[4.5]decane-10-carboxylic acid methyl ester (11c)

Hydrochloride salt of **9a** (65.8 mg, 0.337 mmol) yielded 32.4 mg (43%, 5:1 dr) as a pink oil after column chromatography (trimethylamine deadened silica, 5% methanol/dichloromethane); ^1H NMR (400 MHz, CDCl_3): δ 3.69 (s, 3H), 3.24 (d, $J = 1.0$ Hz, 1H), 3.06 (dq, $J = 10.5$, 6.5, 3.5 Hz, 1H), 2.43 (dd, $J = 13.5$, 10.5 Hz, 1H), 2.31 (ddd, $J = 13.5$, 3.5, 1.0 Hz, 1H), 1.82-1.50 (m, 7H), 1.36 (m, 1H), 1.24 (d, $J = 6.5$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 205.3, 169.9, 69.2, 66.1, 52.3, 49.6, 47.6, 39.2, 36.1, 24.3, 23.7, 22.3 ppm; IR (ATR): ν_{\max} 2957, 1704, 1435, 1329, 1268, 1192, 1158 cm^{-1} ; HRMS (ESI) 226.1440 ($M + \text{H}^+$. $\text{C}_{12}\text{H}_{20}\text{NO}_3$ requires 226.1438).

6-Methyl-8-oxo-5-aza-spiro[3.5]nonane-9-carboxylic acid methyl ester (11d)

Hydrochloride salt of **9a** (72.4 mg, 0.371 mmol) yielded 52.6 mg (67%, 2.5:1 dr) as a yellow oil after column chromatography (trimethylamine deadened silica, 5% methanol/dichloromethane); ^1H NMR (400 MHz, CDCl_3): δ 3.70 (s, 3H), 3.55 (d, $J = 1.0$ Hz, 1H), 2.98 (dq, $J = 10.5$, 6.5, 4.0 Hz, 1H), 2.34 (dd, $J = 13.5$, 10.5 Hz, 1H), 2.27 (ddd, $J = 13.5$, 4.0, 1.0 Hz, 1H), 2.01-1.75 (m, 6H), 1.23 (d, $J = 6.5$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 204.4, 169.1, 65.4, 63.0, 52.3, 48.4, 48.1, 32.4, 31.6, 22.5, 14.4 ppm; IR (ATR): ν_{\max} 2956, 1705, 1434, 1329, 1193, 1166 cm^{-1} ; HRMS (ESI) 212.1275 ($M + \text{H}^+$. $\text{C}_{11}\text{H}_{18}\text{NO}_3$ requires 212.1281).

2-Methyl-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11e)

Hydrochloride salt of **9a** (280 mg, 1.44 mmol) yielded 233 mg (67%, 4.5:1 dr) as a colourless oil after column chromatography (8% ethyl acetate/dichloromethane then 50% ethyl acetate/dichloromethane); ^1H NMR (400 MHz, CDCl_3): δ 3.88 (ddd, $J = 11.5$, 10.0, 3.0 Hz, 1H), 3.72 (ddd, $J = 11.5$, 10.0, 3.0 Hz, 1H), 3.67 (s, 3H), 3.63 (ddd, $J = 11.5$, 11.5, 4.0 Hz, 1H), 3.56 (ddd, $J = 11.5$, 11.5, 4.0 Hz, 1H), 3.26 (d, $J = 1.0$ Hz, 1H), 3.06 (dq, $J = 10.5$, 6.0 Hz, 3.5 Hz, 1H), 2.48 (dd, $J = 13.5$, 10.5 Hz, 1H), 2.30 (ddd, $J = 13.5$, 3.5, 1.0 Hz, 1H), 1.67-1.54 (m, 2H), 1.48-1.36 (m, 2H), 1.25 (d, $J = 6.0$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 205.0, 168.9, 66.8, 63.3, 62.8, 58.2, 52.3, 47.5, 46.9, 36.5, 33.6, 22.8 ppm; IR (ATR): ν_{\max} 2956, 2867, 1703, 1435, 1333, 1162 cm^{-1} ; HRMS (ESI) 242.1386 ($M + \text{H}^+$. $\text{C}_{12}\text{H}_{20}\text{NO}_4$ requires 242.1387).

4-Oxo-2-phenyl-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11f)

Hydrochloride salt of **9b** (116 mg, 0.451 mmol) yielded 105 mg (78%, 7:1 dr) as a yellow oil after successively washing an ethyl acetate layer with water (15 times); ^1H NMR (400 MHz, CDCl_3): δ 7.48-7.27 (m, 5H), 4.11 (dd, $J = 11.0$, 4.0 Hz, 1H), 3.72 (s, 3H), 3.41 (br s, 1H), 3.08 (dd, $J = 13.5$, 11.0 Hz, 1H), 2.53 (ddd, $J = 13.5$, 4.0, 1.0 Hz, 1H), 1.76-1.29 (m, 10H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 205.4, 169.5, 142.5, 128.9, 127.8, 126.7, 66.6, 60.4, 55.5, 52.2, 46.3, 36.6, 33.3, 25.7, 21.5, 21.0 ppm; IR (ATR): ν_{\max} 2930, 2855, 1702, 1434, 1327, 1192, 1162 cm^{-1} ; HRMS (ESI) 302.1754 ($M + \text{H}^+$. $\text{C}_{18}\text{H}_{24}\text{NO}_3$ requires 302.1751).

6-(4-Fluoro-phenyl)-2,2-dimethyl-4-oxo-piperidine-3-carboxylic acid methyl ester (11g)

Hydrochloride salt of **9e** (110 mg, 0.399 mmol) yielded 108 mg (97%, 1.8:1 dr) as a yellow oil without further purification; ^1H NMR (500 MHz, CDCl_3): δ 7.44 (m, 2H), 7.09-7.03 (m, 2H), 4.16 (dd, $J = 11.5$, 3.5 Hz, 1H), 3.75 (s, 3H), 3.33 (d, $J = 1.0$ Hz, 1H), 3.00 (dd, $J = 13.5$, 11.5 Hz, 1H), 2.50 (ddd, $J = 13.5$, 3.5, 1.0 Hz, 1H), 1.24 (s, 3H), 1.21 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 204.7, 169.7, 162.4 (d, $J = 247.0$ Hz), 137.9 (d, $J = 3.5$ Hz), 128.3 (d, $J = 8.5$ Hz), 115.8 (d, $J = 21.5$ Hz), 67.1, 58.0, 56.2, 52.4, 46.0, 28.4, 26.0 ppm; ^{19}F NMR (376 MHz, CDCl_3): δ -114.42 ppm; IR (ATR): ν_{\max} 2969, 1748, 1705, 1603, 1509, 1222,

1195, 1152, 1125 cm^{-1} ; HRMS (ESI) 280.1342 ($\text{M} + \text{Na}^+$, $\text{C}_{15}\text{H}_{19}\text{FNO}_3$ requires 280.1343).

2-(4-Fluoro-phenyl)-4-oxo-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11h)

Hydrochloride salt of **9e** (69.5 mg, 0.248 mmol) yielded 59 mg (75%, 5:1 dr) as a yellow oil after successively washing an ethyl acetate layer with water (5 times); ^1H NMR (400 MHz, CDCl_3): δ 7.46-7.39 (m, 2H), 7.10-7.03 (m, 2H), 4.10 (dd, $J = 11.5, 4.0$ Hz, 1H), 3.73 (s, 3H), 3.41 (br s, 1H), 3.04 (dd, $J = 13.5, 11.5$ Hz, 1H), 2.52 (ddd, $J = 13.5, 4.0, 1.0$ Hz, 1H), 1.80-1.29 (m, 10H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 205.1, 169.6, 162.3 (d, $J = 247.0$ Hz), 138.4 (d, $J = 3.0$ Hz), 128.4 (d, $J = 8.0$ Hz), 115.8 (d, $J = 21.0$ Hz), 66.5, 60.3, 54.8, 52.3, 46.3, 36.6, 33.4, 25.7, 21.6, 21.1 ppm; ^{19}F NMR (376 MHz, CDCl_3): δ -114.7 ppm; IR (ATR): ν_{max} 2933, 2856, 1705, 1600, 1510, 1439, 1329, 1224, 1159 cm^{-1} ; HRMS (ESI) 320.1645 ($\text{M} + \text{H}^+$, $\text{C}_{18}\text{H}_{23}\text{FNO}_3$ requires 320.1656).

2-(4-fluoro-phenyl)-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11i)

Hydrochloride salt of **9e** (129 mg, 0.468 mmol) yielded 84.5 mg (56%, 2:1 dr) as a white solid after column chromatography (trimethylamine deadened silica, 20% ethyl acetate/dichloromethane); mp 110.5-113 $^\circ\text{C}$; ^1H NMR (500 MHz, CDCl_3): δ 7.45-7.40 (m, 2H), 7.11-7.06 (m, 2H), 4.09 (dd, $J = 11.5, 3.5$ Hz, 1H), 3.90 (ddd, $J = 11.5, 10.5, 3.0$ Hz, 1H), 3.81 (ddd, $J = 11.5, 10.5, 3.0$ Hz, 1H), 3.74 (s, 3H), 3.72-3.64 (m, 2H), 3.40 (d, $J = 1.0$ Hz, 1H), 3.06 (dd, $J = 13.5, 11.5$ Hz, 1H), 2.57 (ddd, $J = 13.5, 3.5, 1.0$ Hz, 1H), 2.14 (br s, 1H), 1.81-1.75 (m, 1H), 1.73 (ddd, $J = 14.0, 10.5, 4.0$ Hz, 1H), 1.59 (ddd, $J = 14.0, 10.5, 4.0$ Hz, 1H), 1.52-1.46 (m, 1H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 204.2, 169.0, 162.1 (d, $J = 245.0$ Hz), 138.8 (d, $J = 3.0$ Hz), 128.3 (d, $J = 14.0$ Hz), 115.8 (d, $J = 21.5$ Hz), 67.0, 63.4, 62.8, 58.3, 54.9, 52.5, 46.1, 36.7, 33.4 ppm; ^{19}F NMR (376 MHz, CDCl_3): δ -114.0 ppm; IR (ATR): ν_{max} 2963, 2868, 1706, 1603, 1511, 1223, 1160 cm^{-1} ; HRMS (ESI) 322.1445 ($\text{M} + \text{H}^+$, $\text{C}_{17}\text{H}_{21}\text{FNO}_4$ requires 322.1449), 344.1269 ($\text{M} + \text{Na}^+$, $\text{C}_{17}\text{H}_{21}\text{FNO}_4$ requires 344.1269).

2-(4-Fluoro-phenyl)-4-oxo-9-thia-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11j)

Hydrochloride salt of **9e** (189 mg, 0.686 mmol) yielded 171 mg (63%, 1:1 dr) as a colourless oil after column chromatography (trimethylamine deadened silica, 10-20% ethyl acetate/hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.45-7.39 (m, 2H), 7.11-7.04 (m, 2H), 4.04 (dd, $J = 11.0, 4.0$ Hz, 1H), 3.73 (s, 3H), 3.33 (br s, 1H), 3.22-3.12 (m, 1H), 3.04 (dd, $J = 13.5, 11.0$ Hz, 1H), 3.06-2.93 (m, 1H), 2.56 (ddd, $J = 13.5, 4.0, 0.5$ Hz, 1H), 2.41-2.32 (m, 2H), 2.12-1.93 (m, 2H), 1.84-1.77 (m, 2H), 1.70 (ddd, $J = 14.5, 11.5, 14.5$ Hz, 1H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 204.3, 169.0, 162.4 (d, $J = 247.5$ Hz), 137.8 (d, $J = 3.5$ Hz), 128.3 (d, $J = 8.0$ Hz), 115.8 (d, $J = 21.5$ Hz), 67.4, 59.3, 54.4, 52.5, 45.7, 37.3, 34.3, 23.4, 22.8 ppm; ^{19}F NMR (376 MHz, CDCl_3): δ -114.3 ppm; IR (ATR): ν_{max} 2962, 2922, 1705, 1510,

1226, 1196, 1161 cm^{-1} ; HRMS (ESI) 338.1205 ($\text{M} + \text{H}^+$, $\text{C}_{17}\text{H}_{21}\text{FNO}_3\text{S}$ requires 338.1221).

2-(4-Methoxy-phenyl)-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11k)

Hydrochloride salt of **9f** (757 mg, 2.63 mmol) yielded 290 mg (33%, 2:1 dr) as a pale red solid after column chromatography (0-80% ethyl acetate/cyclohexane); mp 118-121 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 7.43-7.36 (m, 2H), 6.98-6.92 (m, 2H), 4.08 (dd, $J = 11.0, 3.5$ Hz, 1H), 4.03-3.64 (m, 4H), 3.84 (s, 3H), 3.76 (s, 3H), 3.42 (d, $J = 1.0$ Hz, 1H), 3.10 (dd, $J = 13.5, 11.0$ Hz, 1H), 2.57 (ddd, $J = 13.5, 3.5, 1.0$ Hz, 1H-5), 2.15 (br s, 1H), 1.85-1.70 (m, 2H), 1.65-1.44 (m, 2H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 204.4, 168.9, 159.2, 134.1, 127.7, 114.2, 67.0, 63.3, 62.7, 58.2, 55.3, 54.9, 52.3, 46.2, 36.6, 33.3 ppm; IR (ATR): ν_{max} 3318, 2965, 2947, 2865, 1732, 1701, 1515, 1297, 1243, 1159, 1024 cm^{-1} ; HRMS (ESI) 334.1637 ($\text{M} + \text{H}^+$, $\text{C}_{18}\text{H}_{24}\text{NO}_5$ requires 334.1649).

6-(3-pyridyl)-2,2-dimethyl-4-oxo-piperidine-3-carboxylic acid methyl ester (11l)

Hydrochloride salt of **9g** (80 mg, 0.310 mmol) yielded 70 mg (86%, 1.5:1 dr) as a yellow oil without further purification; ^1H NMR (500 MHz, CDCl_3): δ 8.65 (d, $J = 2.0$ Hz, 1H), 8.55 (dd, $J = 4.5, 2.0$ Hz, 1H), 7.80 (ddd, $J = 8.0, 2.0, 2.0$ Hz, 1H), 7.31 (dd, $J = 8.0, 4.5$ Hz, 1H), 4.21 (dd, $J = 11.5, 4.0$ Hz, 1H), 3.73 (s, 3H), 3.13 (d, $J = 1.0$ Hz, 1H), 3.01 (dd, $J = 13.5, 11.5$ Hz, 1H), 2.52 (ddd, $J = 13.5, 4.0, 1.0$ Hz, 1H), 1.24 (s, 3H), 1.22 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 204.3, 169.7, 149.5, 148.8, 137.4, 134.1, 123.9, 66.9, 58.0, 54.2, 52.2, 45.4, 28.3, 25.8 ppm; IR (ATR): ν_{max} 2969, 1707, 1429, 1197, 1153 cm^{-1} ; HRMS (ESI) 263.1393 ($\text{M} + \text{Na}^+$, $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_3$ requires 263.1390).

4-Oxo-2-pyridin-3-yl-9-oxa-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11m)

Hydrochloride salt of **9g** (1.50 g, 5.81 mmol) yielded 1.40 g (79%, 1.5:1 dr) as a yellow oil after column chromatography (50% ethyl acetate/dichloromethane then 100% ethyl acetate); ^1H NMR (400 MHz, CDCl_3): δ 8.69 (d, $J = 2.0$ Hz, 1H), 8.58 (dd, $J = 5.0, 2.0$ Hz, 1H), 7.82 (ddd, $J = 8.0, 2.0, 2.0$ Hz, 1H), 7.34 (dd, $J = 8.0, 5.0$ Hz, 1H), 4.17 (dd, $J = 11.5, 3.5$ Hz, 1H), 3.90 (ddd, $J = 11.5, 11.5, 2.5$ Hz, 1H), 3.81 (ddd, $J = 11.5, 11.5, 2.5$ Hz, 1H), 3.74 (s, 3H), 3.74-3.64 (m, 2H), 3.41 (d, $J = 0.5$ Hz, 1H), 3.09 (dd, $J = 13.5, 11.5$ Hz, 1H), 2.61 (ddd, $J = 13.5, 3.5, 0.5$ Hz, 1H), 2.20 (br s, 1H), 1.83-1.69 (m, 2H), 1.65-1.56 (m, 1H), 1.53-1.45 (m, 1H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 203.5, 168.9, 149.4, 148.7, 137.2, 134.0, 123.8, 67.0, 63.3, 62.7, 58.3, 53.1, 52.5, 45.3, 36.5, 33.2 ppm; IR (ATR): ν_{max} 2952, 2872, 1706, 1428, 1337, 1195, 1166 cm^{-1} ; HRMS (ESI) 305.1486 ($\text{M} + \text{H}^+$, $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_4$ requires 305.1496).

4-Oxo-2-pyridin-3-yl-1,9-diaza-spiro[5.5]undecane-5,9-dicarboxylic acid 9-benzyl ester 5-methyl ester (11n)

Hydrochloride salt of **9g** (145 mg, 0.562 mmol) yielded 145 mg (67%, 2:1 dr) as a yellow oil after column chromatography (50% ethyl acetate/dichloromethane then 100% ethyl acetate);

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^1H NMR (400 MHz, CDCl_3): δ 8.66 (br s, 1H), 8.56 (dd, J = 5.0, 1.5 Hz, 1H), 7.78 (ddd, J = 8.0, 1.5, 1.5 Hz, 1H), 7.37-7.26 (m, 6H), 5.10 (s, 2H), 4.20-4.06 (m, 1H), 3.92-3.75 (m, 2H), 3.71 (s, 3H), 3.45-3.16 (m, 2H), 3.30 (d, J = 0.5 Hz, 1H), 3.07 (dd, J = 13.5, 11.5 Hz, 1H), 2.60 (ddd, J = 13.5, 3.0, 0.5 Hz, 1H), 1.91-1.34 (m, 4H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 203.1, 168.8, 155.2, 149.5, 148.6, 137.0, 136.7, 133.9, 128.6, 128.1, 127.9, 123.8, 67.2, 66.8, 58.8, 53.2, 52.5, 45.0, 39.5, 39.0, 35.5, 32.3 ppm; IR (ATR): ν_{max} 2951, 1694, 1427, 1246, 1164 cm^{-1} ; HRMS (ESI) 438.2032 ($\text{M} + \text{H}^+$, $\text{C}_{24}\text{H}_{28}\text{N}_3\text{O}_5$ requires 438.2023).

4-Oxo-2-pyridin-3-yl-9-thia-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11o)

Hydrochloride salt of **9g** (103.6 mg, 0.402 mmol) yielded 77.5 mg (75%, 0.95:1 dr) as a yellow oil after column chromatography (50% ethyl acetate/hexane then 100% ethyl acetate). ^1H NMR (400 MHz, CDCl_3): δ 8.68-8.64 (m, 1H), 8.58-8.54 (m, 1H), 7.79 (ddd, 8.0, 2.0, 2.0 Hz, 1H), 7.35-7.28 (m, 1H), 4.10 (br s, 1H), 3.71 (s, 3H), 3.33 (d, J = 1.0 Hz, 1H), 3.20-3.09 (m, 1H), 3.05 (dd, 13.5, 11.5 Hz, 1H), 3.06-2.90 (m, 1H), 2.58 (ddd, 13.5, 4.0, 1.0 Hz, 1H), 2.40-2.28 (m, 2H), 2.12-2.05 (m, 1H), 1.82-1.77 (m, 2H), 1.70 (ddd, J = 14.5, 11.5, 3.0, 1H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 203.6, 168.9, 149.5, 148.7, 137.1, 134.0, 123.8, 67.4, 59.3, 52.7, 52.5, 44.9, 37.2, 34.2, 23.3, 22.7 ppm; IR (ATR): ν_{max} 3310, 2952, 2920, 1703, 1424, 1268, 1195, 1162 cm^{-1} ; HRMS (ESI) 321.1260 ($\text{M} + \text{H}^+$, $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$ requires 321.1267).

2-(4-Methyl-thiazol-5-yl)-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11p)

Hydrochloride **9i** (99 mg, 0.356 mmol) yielded 86 mg (75%, 1:1 dr) as an off-white solid after column chromatography (50% ethyl acetate/dichloromethane then 100% ethyl acetate); mp 98-101 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 8.67 (s, 1H), 4.41 (dd, J = 11.0, 3.5 Hz, 1H), 3.90-3.76 (m, 2H), 3.73 (s, 3H), 3.71-3.64 (m, 2H), 3.38 (br s, 1H), 3.05 (dd, J = 13.5, 11.0 Hz, 1H), 2.63 (ddd, J = 13.5, 3.5, 1.0 Hz, 1H), 2.47 (s, 3H), 1.80-1.54 (m, 3H), 1.51-1.41 (m, 1H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 202.5, 168.7, 150.2, 149.9, 133.0, 66.8, 63.3, 62.7, 58.1, 52.6, 48.8, 47.1, 36.5, 33.4, 16.6 ppm; IR (ATR): ν_{max} 2953, 2865, 1706, 1435, 1338, 1255, 1196, 1165 cm^{-1} ; HRMS (ESI) 325.1201 ($\text{M} + \text{H}^+$, $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$ requires 325.1217).

2-(1-Methyl-1H-pyrazol-4-yl)-4-oxo-9-oxa-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11q)

Hydrochloride salt of **9h** (203 mg, 0.776 mmol) yielded 119 mg (50%, 2.5:1 dr) as a yellow oil after column chromatography (0-50% ethanol/ethyl acetate); ^1H NMR (400 MHz, CDCl_3): δ 7.52 (s, 1H), 7.40 (s, 1H), 4.13 (dd, J = 11.0, 3.5 Hz, 1H), 4.00-3.63 (m, 4H), 3.91 (s, 3H), 3.72 (s, 3H), 3.38 (d, J = 1.0 Hz, 1H), 2.97 (dd, J = 13.5, 11.0 Hz, 1H), 2.63 (ddd, J = 13.5, 3.5, 1.0 Hz, 1H), 1.80-1.67 (m, 2H), 1.61-1.44 (m, 2H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 203.7, 168.7, 137.1, 127.6, 123.8, 67.1, 63.2, 62.7, 58.0, 52.3, 47.4, 46.1, 39.0, 36.5, 33.3 ppm; IR (ATR): ν_{max} 3282, 3248, 1704, 1562, 1435, 1296, 1218, 1159 cm^{-1} ; HRMS (ESI) 308.1594 ($\text{M} + \text{H}^+$, $\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}_4$ requires 308.1605).

6-(4-Cyano-phenyl)-8-oxo-5-aza-spiro[3.5]nonane-9-carboxylic acid methyl ester (11r)

Hydrochloride salt of **9j** (102 mg, 0.362 mmol) yielded 67.5 mg (63%, 1:1 dr) as a yellow oil after column chromatography (33% ethyl acetate/hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.69-7.64 (m, 2H), 7.57-7.50 (m, 2H), 4.04 (dd, J = 11.5, 3.5 Hz, 1H), 3.76 (s, 3H), 3.65 (d, J = 1.0 Hz, 1H), 2.86 (dd, J = 13.5, 11.5 Hz, 1H), 2.52 (ddd, J = 13.5, 3.5, 1.0 Hz, 1H), 2.29-2.20 (m, 1H), 2.15-2.05 (m, 1H), 2.04-1.86 (m, 4H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 202.9, 169.0, 147.1, 132.8, 127.5, 118.7, 111.8, 65.1, 63.0, 56.0, 52.5, 46.8, 32.6, 31.7, 14.2; IR (ATR): ν_{max} 3313, 2952, 2227, 1707, 1607, 1435, 1290, 1197, 1165 cm^{-1} ; HRMS (ESI) 299.1383 ($\text{M} + \text{H}^+$, $\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_3$ requires 299.1390).

6-(4-Cyano-phenyl)-8-oxo-2-oxa-5-aza-spiro[3.5]nonane-9-carboxylic acid methyl ester (11s)

Hydrochloride salt of **9j** (93 mg, 0.330 mmol) yielded 42.8 mg (43%, 1.6:1 dr) as a yellow oil after column chromatography (60% ethyl acetate/hexane); ^1H NMR (400 MHz, CDCl_3): δ 7.70-7.66 (m, 2H), 7.57-7.51 (m, 2H), 4.92 (d, J = 7.5 Hz, 1H), 4.61 (d, J = 7.5 Hz, 1H), 4.56 (d, J = 6.5 Hz, 1H), 4.50 (d, J = 6.5 Hz, 1H), 4.02 (dd, J = 11.5, 3.5 Hz, 1H), 3.93 (d, J = 1.5 Hz, 1H), 3.79 (s, 3H), 2.72 (dd, J = 13.5, 11.5 Hz, 1H), 2.56 (ddd, J = 13.5, 3.5, 1.5 Hz, 1H) ppm; ^{13}C -NMR (101 MHz, CDCl_3): δ 200.9, 167.9, 146.3, 132.9, 127.5, 118.6, 112.3, 80.9, 80.1, 62.9, 62.4, 56.1, 53.0, 47.5 ppm; IR (ATR): ν_{max} 3302, 2874, 2228, 1717, 1608, 1441, 1345, 1297 1225 cm^{-1} ; HRMS (ESI) 301.1179 ($\text{M} + \text{H}^+$, $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_4$ requires 301.1183).

General procedure for the synthesis of *N*-Boc imines 12

A suspension of benzenesulfonyl carbamic ester (8.15 mmol), K_2CO_3 (48.9 mmol) and Na_2SO_4 (57.1 mmol) in THF (82 mL) was stirred at reflux for 3h. The mixture was cooled to rt, filtered through a sintered funnel and concentrated *in vacuo*. The imine was used without further purification.

(4-Fluoro-benzylidene)-carbamic acid tert-butyl ester (12e)

Sulfone **7e** (1.12 g, 3.07 mmol), K_2CO_3 (2.54 g, 18.4 mmol) and Na_2SO_4 (3.05 g, 21.5 mmol) gave the title compound (635 mg, 2.86 mmol, 93% yield) as a white solid. Spectroscopic data was identical to that previously reported.¹⁹ ^1H NMR (400 MHz, CDCl_3): δ 8.85 (s, 1H), 7.96-7.90 (m, 2H), 7.18-7.11 (m, 2H), 1.58 (s, 9H) ppm.

(4-Methoxy-benzylidene)-carbamic acid tert-butyl ester (12f)

Sulfone **7f** (1.07 g, 2.84 mmol), K_2CO_3 (2.35 g, 17.0 mmol) and Na_2SO_4 (2.83 g, 19.9 mmol) gave the title compound (601 mg, 2.56 mmol, 90% yield) as a white solid. Spectroscopic data was identical to that previously reported.¹⁹ ^1H NMR (400 MHz, CDCl_3): δ 8.87 (s, 1H), 7.91-7.85 (m, 2H), 6.98-6.91 (m, 2H), 3.86 (s, 3H), 1.57 (s, 9H) ppm.

(4-Methyl-thiazol-5-ylmethylene)-carbamic acid tert-butyl ester (12h)

Sulfone **7h** (3.00 g, 8.15 mmol), K_2CO_3 (6.75 g, 48.9 mmol) and Na_2SO_4 (8.11 g, 57.1 mmol) gave the title compound (1.81 g, 8.07 mmol, 99% yield) as an orange oil. 1H NMR (400 MHz, $CDCl_3$): δ 9.17 (d, J = 0.5 Hz, 1H), 8.88 (s, 1H), 2.68 (s, 3H), 1.55 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3, 161.8, 161.7, 158.2, 129.7, 82.7, 27.8, 16.3 ppm; IR (ATR): ν_{max} 2982, 2931, 1705, 1600, 1512, 1366, 1243, 1150 cm^{-1} ; HRMS (ESI) 281.0917 ($M + Na^+$. $C_{11}H_{18}N_2NaO_3S$ requires 281.0930 for the methanol adduct).

(4-Cyano-benzylidene)-carbamic acid tert-butyl ester (12j)

Sulfone **7j** (1.15 g, 3.13 mmol), K_2CO_3 (2.59 g, 18.8 mmol) and Na_2SO_4 (3.11 g, 21.9 mmol) gave the title compound (723 mg, 3.13 mmol, 100% yield) as a white amorphous solid. Spectroscopic data was identical to that previously reported.²⁰ 1H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.03-7.97 (m, 2H), 7.79-7.74 (m, 2H), 1.58 (s, 9H) ppm.

(4-Trifluoromethyl-benzylidene)-carbamic acid tert-butyl ester (12k)

Sulfone **7k** (1.09 g, 2.63 mmol), K_2CO_3 (2.18 g, 15.8 mmol) and Na_2SO_4 (2.61 g, 18.4 mmol) gave the title compound (710 mg, 2.60 mmol, 99% yield) as a white amorphous white solid. Spectroscopic data was identical to that previously reported.¹⁹ 1H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H), 1.59 (s, 9H) ppm.

General procedure for the one-pot synthesis of 2-spiropiperidines 11

Neat $TiCl_4$ (4.56 mmol) was added dropwise to a solution of imine (1.14 mmol) in CH_2Cl_2 (11.4 mL) at $-78^\circ C$. Chan's diene (2.28 mmol) was added dropwise and the mixture was stirred for 30 mins at $-78^\circ C$. MeOH (18.2 mmol) was added and the mixture was stirred at rt for 4h. Ketone (5.70 mmol) and $NaHCO_3$ (45.6 mmol) were sequentially added, and the reaction was stirred overnight at rt. The reaction was quenched with 1.59M citric acid in MeOH (11.4 mmol), and the mixture was cooled to $0^\circ C$. Water (8 mL) was carefully added, followed by dilution with CH_2Cl_2 (10 mL) and the mixture was stirred vigorously for 30 mins at rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). Organics were combined, washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography.

2-(4-Methyl-thiazol-5-yl)-4-oxo-9-thia-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11t)

Imine **12h** (149 mg, 0.659 mmol), $TiCl_4$ (289 μL , 2.64 mmol), Chan's diene (343 mg, 1.32 mmol), MeOH (424 μL , 10.5 mmol), tetrahydro-4H-thiopyran-4-one (383 mg, 3.30 mmol) and $NaHCO_3$ (2.22 g, 26.4 mmol). Purification by column chromatography (40% EtOAc/hexane) gave the title compound (123 mg, 0.362 mmol, 55% yield) as a red oil; 1H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1H), 4.43-4.32 (m, 1H), 3.72 (s, 3H), 3.31 (br. s, 1H), 3.16-3.06 (m, 1H), 3.02 (dd, J = 13.7, 11.5 Hz, 1H),

3.05-2.94 (m, 1H), 2.62 (ddd, J = 13.7, 3.5, 1.0 Hz, 1H), 2.48 (s, 3H), 2.42-2.33 (m, 2H), 2.12-1.75 (m, 4H), 1.71 (ddd, J = 14.5, 11.7, 3.2 Hz, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.6, 168.7, 150.3, 149.8, 133.1, 67.2, 59.1, 52.6, 48.4, 46.9, 37.2, 34.3, 23.3, 22.7, 15.7 ppm; IR (ATR): ν_{max} 3314, 2952, 2922, 1705, 1434, 1415, 1315, 1266, 1196, 1163 cm^{-1} ; HRMS (ESI) 341.0990 ($M + H^+$. $C_{15}H_{21}N_2O_3S_2$ requires 341.0988).

2-(4-Methyl-thiazol-5-yl)-4-oxo-1,9-diaza-spiro[5.5]undecane-5,9-dicarboxylic acid 9-benzyl ester 5-methyl ester (11u)

Imine **12h** (119 mg, 0.527 mmol), $TiCl_4$ (231 μL , 2.11 mmol), Chan's diene (260 mg, 1.05 mmol), MeOH (341 μL , 8.43 mmol), 1-Z-4-piperidone (615 mg, 2.64 mmol) and $NaHCO_3$ (1.77 g, 21.1 mmol). Purification by column chromatography (40% EtOAc/hexane then 80% EtOAc/hexane) gave the title compound (107 mg, 0.473 mmol, 45% yield) as an orange oil; 1H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1H), 7.39-7.27 (m, 5H), 5.11 (s, 2H), 4.46-4.33 (m, 1H), 3.95-3.76 (m, 2H), 3.73 (s, 3H), 3.43-3.24 (m, 2H), 3.29 (br. s, 1H), 3.05 (dd, J = 13.5, 11.2 Hz, 1H), 2.70-2.60 (m, 1H), 2.46 (s, 3H), 2.04 (br. s, 1H), 1.93-1.37 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.3, 168.7, 155.2, 150.3, 149.9, 136.7, 132.9, 128.6, 128.2, 128.1, 67.3, 66.7, 58.5, 52.7, 48.9, 47.0, 39.5, 39.1, 35.6, 32.4, 15.7 ppm; IR (ATR): ν_{max} 2951, 1698, 1432, 1247, 1165 cm^{-1} ; HRMS (ESI) 458.1747 ($M + H^+$. $C_{23}H_{28}N_3O_5S$ requires 458.1744).

2-(4-Cyano-phenyl)-4-oxo-1,9-diaza-spiro[5.5]undecane-5,9-dicarboxylic acid 9-benzyl ester 5-methyl ester (11v)

Imine **12j** (131 mg, 0.570 mmol), $TiCl_4$ (250 μL , 2.28 mmol), Chan's diene (296 mg, 1.14 mmol), MeOH (368 μL , 9.12 mmol), 1-Z-4-piperidone (664 mg, 2.85 mmol) and $NaHCO_3$ (1.92 g, 22.8 mmol). Purification by column chromatography (30% EtOAc/hexane) gave the title compound (62 mg, 0.137 mmol, 24% yield) as a yellow oil; 1H NMR (400 MHz, $CDCl_3$): δ 7.71-7.64 (m, 2H), 7.59-7.52 (m, 2H), 7.39-7.28 (m, 5H), 5.10 (s, 2H), 4.19-4.08 (m, 1H), 3.92-3.75 (m, 2H), 3.73 (s, 3H), 3.46-3.34 (m, 1H), 3.32 (d, J = 1.0 Hz, 1H), 3.32-3.18 (m, 1H), 3.03 (dd, J = 13.7, 11.5 Hz, 1H), 2.61 (dd, J = 13.7, 3.5 Hz, 1H), 1.89-1.37 (m, 4H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.0, 169.0, 155.2, 146.8, 136.7, 132.8, 128.6, 128.2, 128.0, 127.5, 118.6, 112.0, 67.3, 66.7, 58.9, 55.0, 52.6, 45.2, 39.5, 39.0, 35.6, 32.3 ppm; IR (ATR): ν_{max} 2952, 2227, 1694, 1431, 1231, 1164, 1120 cm^{-1} ; HRMS (ESI) 462.2025 ($M + H^+$. $C_{26}H_{28}N_3O_5$ requires 462.2023), 484.1841 ($M + Na^+$. $C_{26}H_{27}N_3NaO_5$ requires 484.1843).

4-Oxo-2-(4-trifluoromethyl-phenyl)-1-aza-spiro[5.5]undecane-5-carboxylic acid methyl ester (11w)

Imine **12k** (314 mg, 1.15 mmol), $TiCl_4$ (504 μL , 4.60 mmol), Chan's diene (598 mg, 2.30 mmol), MeOH (743 μL , 18.4 mmol), cyclohexanone (595 μL , 5.75 mmol) and $NaHCO_3$ (3.86 g, 46.0 mmol). Purification by column chromatography (10% EtOAc/hexane) gave an inseparable mixture of product and cyclohexanone. The mixture was dissolved in EtOAc (20 mL) and washed with water (10 x 10 mL), dried ($MgSO_4$), filtered and concentrated to give the title compound (117 mg, 0.322 mmol, 28% yield) as a yellow oil; 1H NMR (400 MHz, $CDCl_3$): δ

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7.67-7.55 (m, 4H), 4.18 (dd, $J = 11.2, 3.8$ Hz, 1H), 3.73 (s, 3H), 3.42 (br. s, 1H), 3.06 (dd, $J = 13.5, 11.2$ Hz, 1H), 2.57 (ddd, $J = 13.5, 3.8, 1.0$ Hz, 1H), 1.78-1.29 (m, 10H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 204.6, 169.5, 146.4, 130.0 (q, $J = 32.4$ Hz), 127.1, 125.9 (q, $J = 3.5$ Hz), 124.1 (q, $J = 273$ Hz), 66.6, 60.3, 54.9, 52.3, 45.8, 36.6, 33.3, 25.6, 21.5, 21.0 ppm; ^{19}F NMR (376 MHz, CDCl_3): δ -62.4 ppm; IR (ATR): ν_{max} 2933, 2857, 1706, 1324, 1164, 1123, 1068 cm^{-1} ; HRMS (ESI) 370.1606 ($\text{M} + \text{H}^+$, $\text{C}_{19}\text{H}_{23}\text{F}_3\text{NO}_3$ requires 370.1625).

2,2-Dimethyl-6-(4-methyl-thiazol-5-yl)-4-oxo-piperidine-3-carboxylic acid methyl ester (11x)

Imine **12h** (321 mg, 1.42 mmol), TiCl_4 (623 μL , 5.68 mmol), Chan's diene (738 mg, 2.84 mmol), MeOH (917 μL , 22.7 mmol), acetone (630 μL , 8.52 mmol) and NaHCO_3 (4.77 g, 56.8 mmol). Purification by column chromatography (75% EtOAc/hexane) gave the title compound (96 mg, 0.341 mmol, 24% yield) as a red solid; mp 101.5-106 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 8.64 (s, 1H), 4.62 (dd, $J = 11.0, 3.5$ Hz, 1H), 3.74 (s, 3H), 3.61 (s, 1H), 2.59 (dd, $J = 13.5, 3.5$ Hz, 1H), 2.43-2.40 (m, 1H), 2.41 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3): δ 202.3, 168.4, 151.2, 148.7, 134.1, 66.9, 56.8, 52.0, 49.5, 48.9, 30.0, 22.7, 15.5 ppm; IR (ATR): ν_{max} 2953, 1747, 1713, 1435, 1341, 1276, 1192, 1121 cm^{-1} ; HRMS (ESI) 283.1112 ($\text{M} + \text{H}^+$, $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ requires 283.1111).

Conflicts of interest

There are no conflicts to declare.

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Notes and references

† X-ray crystal structure of **11i** with thermal ellipsoids shown at 50%. CCDC 1549997 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

- 1 S. D. Griggs, D. T. Tape and P. A. Clarke, *Org. Biomol. Chem.* 2018, review companion paper.
- 2 J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters and B. Witkop, *Proc. Natl. Acad. Sci. USA* 1971, **68**, 1870-1875.
- 3 a) Y. Hirasawa, H. Morita, and J. Kobayashi, *Org. Lett.* 2004, **6**, 3389-3391. b) Y. Hirasawa, J. Kobayashi, Y. Obara, N. Nakahata, N. Kawahara, Y. Goda, H. Morita, *Heterocycles* 2006, **68**, 2357-2364.
- 4 T. Chou, M. Kuramoto, Y. Otani, M. Shikano, K. Yazawa, D. Uemura, *Tetrahedron Lett.* 1996, **37**, 3871-3874.
- 5 F. Voss, S. Schunk and H. Steinhagen, *RSC Drug Discovery Series* 2016, **50**, *Privileged Scaffolds in Medicinal Chemistry: Design, Synthesis, Evaluation*, 439-458, Ed. S. Bräse.

- 6 Y. Troin and M. E. Sinibaldi, *Targets in Heterocyclic Systems: Chemistry and Properties*, Italian Chemical Society (Rome), 2009, **13**, 120-146.
- 7 W.-Y. Siau and J. W. Bode, *J. Am. Chem. Soc.* 2014, **136**, 17726-17729.
- 8 R. J. Bahde and S. D. Rychnovsky, *Org. Lett.*, 2008, **10**, 4017-4020.
- 9 X. Cheng and S. Waters, *Org. Lett.*, 2010, **12**, 205-207.
- 10 P. A. Clarke, A. V. Zaytsev and A. C. Whitwood, *Tetrahedron Lett.* 2007, **48**, 5209-5212.
- 11 P. A. Clarke, A. V. Zaytsev and A. C. Whitwood, *Synthesis* 2008, 3530-3532.
- 12 P. A. Clarke, A. V. Zaytsev, T. W. Morgan, A. C. Whitwood and C. Wilson, *Org. Lett.* 2008, **10**, 2877-2880.
- 13 G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.* 1963, **85**, 207-222.
- 14 S. D. Griggs, N. Thompson, D. T. Tape, M. Fabre and P. A. Clarke, *Chem. Eur. J.* 2017, **23**, 9262-9265.
- 15 S. N. Huckin, L. Weiler, *Tetrahedron Lett.* 1971, **50**, 4835-4838.
- 16 a) P. A. Clarke, S. Santos and W. H. C. Martin, *Green Chem.* 2007, **9**, 438-440. b) P. A. Clarke, S. Santos, N. Mistry, L. Burroughs and A. C. Humphries, *Org. Lett.* 2011, **13**, 624-627.
- 17 a) P. A. Clarke, W. H. C. Martin, J. M. Hargreaves, C. Wilson and A. J. Blake, *Org. Biomol. Chem.* 2005, **3**, 3551-3563. b) P. A. Clarke, W. H. C. Martin, J. M. Hargreaves, C. Wilson and A. J. Blake, *Chem. Comm.* 2005, 1061-1063.
- 18 A. C. Brown and L. A. Carpino, *J. Org. Chem.* 1985, **50**, 1749-1750.
- 19 L. Huang and W. D. Wulff, *J. Am. Chem. Soc.* 2011, **133**, 8892-8895.
- 20 A. S. Tsai, M. E. Tauchert, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.* 2011, **133**, 1248-1250.
- 21 D. Best, S. Kujawa and H. W. Lam, *J. Am. Chem. Soc.* 2012, **134**, 18193-18196.
- 22 For GSK compounds for lead oriented synthesis, contact free.buildingblocks@gsk.com
- 23 J. S. Bandar and T. H. Lambert, *J. Am. Chem. Soc.* 2013, **135**, 11799-11802.
- 24 R. C. F. Jones, C. C. M. Law and M. R. J. Elsegood, *ARKIVOC*, 2013, **3**, 81-97.
- 25 C. Rampalagos and W. D. Wulff, *Adv. Synth. Catal.* 2008, **350**, 1785-1790.